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Attorney Docket No. 100717-660
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| APPLICANT | : | Christoph METHFESSEL et al |
| SERIAL NO. | : | 10/523,784 |
| CUSTOMER NO. | : | 27384 |
| FILED | : | April 8, 2005 |
| FOR | : | DEVICE AND METHODS FOR CARRYING OUT ELECTRICAL MEASUREMENTS ON MEMBRANE BODIES |
| ART UNIT | : | 1641 |
| EXAMINER | : | Leon Yun Bon Lum |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**APPELLANTS' BRIEF ON APPEAL PURSUANT TO 37 CFR § 41.37**

SIR:

This is an appeal from the final rejection of claims 11-13 and 15-17.

## (1) REAL PARTY IN INTEREST

The real party in interest is Bayer Technology Services GmbH by virtue of an assignment recorded in the United States Patent and Trademark Office on April 29, 2005, at Reel 016184/Frame 0675.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

## (3) STATUS OF CLAIMS

The application was originally filed with claims 1-10. The preliminary amendment filed February 9, 2005, canceled claims 1-10 and added new claims 11-20. Subsequently, the Examiner required restriction and, as a result of Appellants' elections, claims 11-13 and 15-17 were considered and examined, whereas claims 14 and 18-20 were withdrawn from consideration. This appeal is taken as to the final rejection of claims 11-13 and 15-17.

## (4) STATUS OF AMENDMENTS

There have not been any amendments after the final rejection.

## (5) SUMMARY OF THE CLAIMED SUBJECT MATTER

There is a single independent claim, viz., claim 11, which relates to a measuring arrangement for measuring an electrical signal on a membrane body, comprising:

a) an electrical measuring instrument;

b) electrodes;

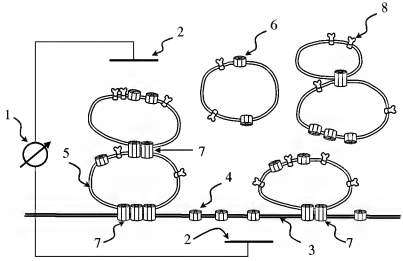
c) a membrane comprising at least one connexin or innexin; and

d) a membrane body comprising at least one connexin or innexin;

wherein the connexins and/or innexins in the membrane and membrane body cooperate to form at least one gap junction channel, and an electrically conducting access is produced from a side of the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

Claim 11 is supported by, for example, item 1 at the top of page 12 of the instant specification.

For the convenience of the Board, Figure 1 is reproduced below:




Referring to the figure, the measuring arrangement comprises *electrical measuring instrument* **1** [claim 11, element a)], *electrodes* **2** (one above and one below **1**) [claim 11, element b)], a *membrane* **3** itself comprising connexins or innexins **4** [claim 11, element c)] and a

*membrane body* **5** likewise comprising connexins or innexins **6** [claim 11, element d)]. The connexins and innexins **4** in the membrane **3** cooperate with the connexins and innexins **6** in the membrane body **5** to form a *gap junction channel* **7**. An electrically conducting access is produced from a side of the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

## (6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The ground(s) of rejection to be reviewed on appeal are:

(1) The rejection of claims 11, 12 and 15-17 under 35 USC § 103(a) as being obvious over Mazet et al. ("Mazet"), *Eur. J. Biochem., 210:* 249-256 (1992), in view of Barbier et al. ("Barbier"), US 2004/0126817.

(2) The rejection of claim 13 under 35 USC § 103(a) as being obvious over Mazet in view of Barbier as applied to claim 11 and further in view of Xu et al. ("Xu"), US 5,874,668.

## (7) ARGUMENT

### I. THE COMBINATION OF MAZET AND BARBIER DOES NOT MAKE OUT A *PRIMA FACIE* CASE OF THE OBVIOUSNESS OF ANY OF CLAIMS 11-13 AND 15-17.

Appellants respectfully submit that the combination of Mazet and Barbier does not make out a *prima facie* case of the obviousness of the rejected claims.

Main claim 11 is directed to a measuring arrangement for measuring an electrical signal on biological membrane bodies, whereby an electroconductive access into the membrane body is created by gap junction channels.

According to paragraph [0025] of the specification, published as US 2005/0027139, the object of the present invention is to develop improved methods for carrying out electrochemical studies on membrane bodies.

According to paragraph [0039], "membrane bodies" in the context of the invention are volume elements filled with a liquid and enclosed by a membrane; membrane bodies according to the invention are preferably biological membrane bodies, e.g. living cells.

According to paragraph [0026], the electrical measurements allow conclusions to be drawn about the state and the behavior of membrane-integrated biomolecules, and about their reaction to prospective effector molecules.

According to claim 11, the measuring arrangement for measuring an electrical signal on a membrane body, comprises:

a) an electrical measuring instrument;

b) electrodes;

c) a membrane comprising at least one connexin or innexin; and

d) a membrane body comprising at least one connexin or innexin;

wherein the connexins and/or innexins in the membrane and membrane body cooperate to form at least one gap junction channel, and an electrically conducting access is produced from a side of

the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

Thus, gap junctions between a membrane and a membrane body are used to produce an electrically conducting access to an interior of the membrane body in order to gain insight into the behavior of membrane-integrated biomolecules.

Mazet deals with the characterization of gap junctions per se. To quote Mazet (page 210, left column): "*The question is how to correlate the activity of the channel to its structure. In the present report, we have focused on voltage-dependent gating properties.*" So, Mazet's objective is totally different from the objective of the present invention. Appellants respectfully submit that a person having ordinary skill in the art would not have consulted Mazet in order to find improved methods for carrying out electrochemical studies on membrane bodies, particularly since Mazet does not deal with membrane bodies in at all.

Furthermore, Mazet did not disclose a measuring arrangement for measuring an electrical signal on a membrane body, as required by claims 11, 12 and 15-17. Mazet discloses a measuring arrangement for measuring an electrical signal on a membrane. More specifically, Mazet describes a planar bilayer that is initially devoid of connexins or gap junctions. In a second stage, a proteoliposome preparation containing connexin is incorporated into the planar bilayer, thus producing a bilayer that does contain connexin. Subsequently, Mazet studies the electrical properties, specifically the conductance and the voltage dependence, of the bilayer and of the connexins incorporated therein. There is no teaching or suggestion in Mazet to measure an electrical signal on a membrane body.

The measuring arrangement required by instant claim 11 is much more complex than the measuring configuration disclosed by Mazet. Besides a membrane, the measuring arrangement according to claim 11 contains a membrane body comprising at least one connexin or innexin. Furthermore, the connexins and/or innexins in the membrane and membrane body cooperate to form at least one gap junction channel, and an electrically conducting access is produced from a side of the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

Mazet does not teach or suggest using the bilayer therein with its incorporated connexins as a substrate for more complex configurations, or for a purpose other than to study the properties of the connexons or gap junctions themselves.

Further, Mazet would not have motivated persons skilled in the art to enhance Mazet's measuring configuration in order to study membrane bodies instead of gap junctions.

In fact it is highly questionable, as will be explained in greater detail below, whether the bilayer disclosed by Mazet could be used for studying membrane bodies at all.

Barbier does not heal the above-noted deficiencies of Mazet. Consequently, the combination of Mazet and Barbier fails to make out a *prima facie* case of the obviousness of any of claims 11, 12 and 15-17.

Barbier describes an assay involving two types of cells, both containing connexins, and a biochemical signal transfer through the gap junctions. Barbier's concept differs from the present invention in several decisive aspects:

(1) Barbier discusses only gap junctions formed between two cells; nowhere does Barbier suggest that one side of the gap junction may be formed from a lipid bilayer other than a living cell membrane.

(2) Barbier restricts itself entirely to biochemical or optical detection methods, for the simple reason that the method described therein does not allow any direct electrical measurement from the paired cells.

(3) Barbier employs the measuring configuration described therein solely for the purpose of investigating the gap junction proteins themselves, for example; to detect ligands that alter the properties of the gap junctions; nowhere does Barbier teach or suggest the use of gap junctions as a tool to investigate the properties of membrane bodies.

Thus, a person having ordinary skill in the art would not have considered Barbier in finding a solution to the technical problem sought to be solved with the arrangement provided by claim 11: development of improved methods for carrying out electrochemical studies on membrane bodies. Instead, Barbier clearly deals with, and, therefore, would have been considered to be limited to "a gap junction assay method and methods for both characterizing connexins and for identifying compounds that affect gap junction function."

However, even assuming, merely for the sake of argument, that a person having ordinary skill in the art would have considered Barbier, such a person would not have found any teaching or suggestion for improved electrochemical studies on membrane bodies, since Barbier does not mention electrochemical studies on membrane bodies at all.

Moreover, a person having ordinary skill in the art would not have been motivated to combine the disclosures of Mazet and Barbier in the first place since Mazet deals with electrical measurements and Barbier deals with optical measurements.

And even if one ordinary skill in the art did combine the disclosures of Barbier and Mazet, such a person would never have achieved the subject matter of claim 11 or any of the other rejected claims, as both references deal with characterization of gap junctions and not with the characterization of membrane bodies by using gap junctions.

Thus, persons skilled in the art would have had no reasonable expectation of success in the proposed combination, even if, assuming for the sake of argument, there was some teaching or suggestion or other evidence of motivation to carry it out. It is not true, as the Examiner apparently implies, that it would have been expected to be a simple, straight-forward modification to place a cell in contact with Mazet's lipid bilayer. Quite the contrary, a reasonable expectation of success was entirely lacking. A free standing lipid bilayer, as described by Mazet, is by nature a fragile and instable structure (like a soap bubble), and a person having ordinary skill in the art would have been reasonable to expect that, if a cell is placed on or near it, the bilayer would deform or rupture long before any connexins found each other and interacted to form a stable gap junction (like a soap bubble usually bursts when it lands on the ground). Indeed, this is why the present application proposes to use a mechanically more stable, suspended or supported bilayer as a substrate for the measuring configuration.

In view of the foregoing, Appellants respectfully submit that the combination of Mazet and Barbier does not make out a *prima facie* case of the obviousness of any of claims 11, 12 and 15-17.

## II. THE COMBINATION OF MAZET AND BARBIER FURTHER IN VIEW OF XU DOES NOT MAKE OUT A *PRIMA FACIE* CASE OF THE OBVIOUSNESS OF CLAIM 13

Appellants respectfully point out that this rejection was dependent upon the combination of Mazet and Barbier making out a *prima facie* case of the obviousness of the basic aspects of the present invention, which, Appellants have explained above is not, in fact, the case. There is nothing in the combination of Mazet and Barbier with Xu that overcomes the deficiencies in the combination of Mazet and Barbier. Indeed, Xu is relied upon to teach a reconstituted membrane at the end of a patch clamp electrode. Xu does not remedy the fact that, as indicated previously, Mazet and Barbier are not properly combinable; that Mazet and Barbier deal with different types of measurements, one electrical and one optical, and, therefore, even if combined would not achieve the present arrangement; or that the combination of Mazet and Barbier fails to reveal a reasonable expectation of success in coupling a membrane body to Mazet's membrane. Consequently, Appellants respectfully submit that the combination of Mazet, Barbier and Xu also fails to make out a *prima facie* case of the obviousness of claim 13.

Appellants further submit that Xu is completely irrelevant to the instant subject matter. While it is true that Xu forms a lipid bilayer on the tip of a patch pipette, this in itself is definitely very early prior art, having been described in the 1980's by numerous authors. Moreover, Xu

employs this configuration only to provide certain membrane proteins (including, for the purpose of illustration, a connexin) in a bilayer for the purpose of atomic force microscopy, which is a completely different method and pursues completely different goals from the electrical assays described in the present application.

In view of the foregoing, Appellants respectfully request that the Honorable Board reverse the final rejections.

## AUTHORIZATION TO CHARGE FILING FEE TO DEPOSIT ACCOUNT

It is requested that the fee for the filing of the Brief on Appeal be charged to the undersigned's Deposit Account No. 14-1263 in the amount of $540.00 for other than a small entity.

## CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, appellant requests that this be considered a petition therefor. Please charge the required Petition fee to Deposit Account No. 14-1263.

## ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess to our Deposit Account No. 14-1263.

Respectfully submitted,

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## (8) CLAIMS APPENDIX

CLAIMS ON APPEAL

11. A measuring arrangement for measuring an electrical signal on a membrane body, comprising:

a) an electrical measuring instrument;

b) electrodes;

c) a membrane comprising at least one connexin or innexin; and

d) a membrane body comprising at least one connexin or innexin;

wherein the connexins and/or innexins in the membrane and membrane body cooperate to form at least one gap junction channel, and an electrically conducting access is produced from a side of the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

12. The measuring arrangement according to claim 11, wherein the membrane is configured as a supported bilayer.

13. The measuring arrangement according to claim 11, wherein the membrane covers an end of a capillary.

15. A method for measuring an electrical signal on a biological membrane body, comprising:

a) providing a measuring arrangement according to claim 11; and

b) measuring an electrical signal on the membrane body.

16. The method according to claim 15, wherein the electrical signal is at least one signal selected from the group consisting of:

a) the membrane potential of the membrane body;

b) the electrical current flowing through the membrane; and

c) the electrical capacitance of the membrane.

17. A method for identifying an active agent that affects a property of a receptor and/or ion channel, comprising:

a) providing a measuring arrangement according to claim 11, wherein the membrane body comprises a receptor and/or ion channel;

b) bringing the membrane body into contact with at least one test substance;

c) measuring at least one electrical signal on the membrane body; and

d) determining whether the at least one electrical signal has been affected by the presence of the at least one test substance, wherein an effect on the electrical signal by the test substance is taken as an indication that the test substance is an active substance.

## (9) EVIDENCE APPENDIX

NONE

## (10) RELATED PROCEEDINGS APPENDIX

NONE